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EDITORIAL

Alport syndrome and thin basement membrane nephropathy: Unraveling the tangled strands of type IV collagen

A trimer consisting of two α1 chains and one α2 chain of type IV collagen ($[\alpha1]_2[\alpha2](IV)$) is an essential component of basement membranes including the subendothelial layer of the glomerular basement membrane (GBM) [1]. In contrast to the ubiquity of $[\alpha1]_2[\alpha2](IV)$, the α3, α4, and α5 chains of type IV collagen are found in few specific sites: the basement membranes of glomeruli and distal tubules, neuromuscular junctions, eye, ear, lung, and seminiferous tubules. $[\alpha1]_2[\alpha2](IV)$ is present at all stages of development. During nephrogenesis, collagen α3, α4, and α5 chains appear at the capillary loop stage of glomerular development [2], and the α3α4α5(IV) trimer progressively replaces $[\alpha1]_2[\alpha2](IV)$ as the dominant constituent of GBM collagen. Laminin, another major component of the GBM, shows a similar ontogenetic transition from laminin A,B1,B2 to A,S,B2 that parallels the switch from $[\alpha1]_2[\alpha2](IV)$ to α3α4α5(IV) [3].

Mutations in any of the α3-5(IV) chains may impair formation of the α3α4α5(IV) heterotrimer that forms the major part of the lamina densa interna in postnatal life [4]. In Alport syndrome (AS), the GBM is initially uniformly thin, but then proteolysis and attempted reconstruction with $[\alpha1]_2[\alpha2](IV)$ produce a thickened and multilayered GBM. In thin basement membrane nephropathy (TBMN), the ultrastructural appearance is initially indistinguishable from Alport syndrome, but progressive disruption of the basement membrane, renal insufficiency, and extrarenal manifestations do not occur. The condition is common, and occurs in at least 1% of the population.

The Melbourne group has previously shown that hematuria segregates with the *COL4A3*/*COL4A4* locus on chromosome 2 in up to 36% of families with TBMN [5]. Mutations in *COL4A3* [6, 7] and *COL4A4* [7, 8] can cause autosomal-recessive Alport syndrome. In this issue of *Kidney International*, Wang et al [9] describe a systematic examination for mutations of the *COL4A3* gene in 62 individuals with clinical or biopsy evidence of thin glomerular basement membrane disease. Most of the subjects had previously been examined for mutations in *COL4A4*. This adds to the growing evidence yoking mutations in these genes to TBMN [10–14].

Key words: type IV collagen, Alport syndrome, thin basement membrane nephropathy.

Heterozygosity for a *COL4A3* or *COL4A4* mutation causes thin glomerular basement membrane disease, and homozygosity or mixed heterozygosity causes autosomal-recessive Alport syndrome [14]. This can be understood as a "dose effect:" presence of one normal allele results in less α3α4α5(IV) formation, absence of a normal allele, and a lack of α3α4α5(IV). With loss of one allele, the resulting lamina densa is thin, but seemingly resistant to proteolysis. As might be expected, a mutation in each of *COL4A3* and *COL4A4* has not turned out to be an appreciable cause of Alport syndrome: one normal allele of each chain remains. Occasional families with a single *COL4A3* or a *COL4A4* mutation do develop renal failure, usually in adult life [11, 15, 16]. This may signify that some mutations are more deleterious than others, or that other modifying effects are involved. At first sight, these cases of autosomal-dominant Alport syndrome might be thought analogous to women heterozygous for X-linked Alport syndrome, some of whom eventually develop renal failure and extrarenal manifestations. The analogy is not exact, however, because lyonization in females heterozygous for a *COL4A5* mutation ensures that some mosaic domains possess, and others lack, normal α5 chains, and thus, α3α4α5(IV), rather than there being an overall quantitative reduction in α3α4α5(IV). Further research is needed to extend the generality of these findings about *COL4A3* and *COL4A4* mutations, and to identify other hereditary abnormalities of the GBM.

The spectrum of hereditary type IV collagen nephropathies thus spans from TBMD (*COL4A3* or *COL4A4* heterozygotes), in which renal function typically declines no faster than the population mean, to severe forms of AS, with renal failure in childhood (*COL4A5* male hemizygotes and *COL4A3* and *COL4A4* homozygotes or mixed heterozygotes). As is so common in medicine, milder forms are more frequent, but more severe forms attract more attention. Intermediate in severity are the adult forms of Alport syndrome. In the United States these forms appear less frequent than TBMD but more frequent than juvenile forms of AS. Adult-type Alport syndrome may remain undiagnosed because renal failure occurs in adult life with little to distinguish it from advanced glomerulonephritis. Diagnosis is particularly treacherous because the largest family, with apparently several thousand gene carriers, does not have prominent hearing loss [17].

A real conundrum for the pediatric nephrologist who must give a prognosis to parents of children with hematuria is distinguishing TBMN from adult types of Alport syndrome. Unless there is a clear family history of renal failure, even biopsy and follow-up for several years cannot distinguish between these two. Microhematuria is not constantly present in TBMN [8], sporadic hematuria in females can obscure the picture, and clinical pedigree analysis rarely suffices to distinguish the mode of inheritance with certainty. Confident reassurance about the benign nature of the nephropathy may later prove cruelly misplaced. We have encountered this tragedy in families belatedly shown to have *COL4A5* mutations or renal failure in the extended family. Misdiagnosis of Alport syndrome as TBMN may be quite common: 10% of families with a biopsy diagnosis of TBMN showed linkage to the *COL4A5* locus, suggesting that they were really families with Alport syndrome [5]. The ultimate solution to this problem lies in genetic diagnosis, but at present this is not readily available. Even if it were available, the currently low detection rate for mutations would limit its usefulness. Right now, the best a practicing clinician can do is take a detailed and persistent family history, particularly looking for severely affected males on the mother's side of the family, and to bear in mind that a clinical and biopsy diagnosis of TBMN is fallible unless the family contains several examples of elderly hematuric males with normal renal function.

If real suspicion arises concerning the possibility of an adult type of Alport syndrome in a young person with hematuria, or if a patient with hematuria in a family putatively affected with TBMN is being evaluated as a renal donor, analysis for a C1564S or L1649R mutation in *COL4A5* is reasonable and available in the United States. At present, more widespread screening for collagen IV gene mutations does not appear justified.

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